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CONDEA VISTA

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June 25, 1996

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

ATTN: 8(e) Coordinator

ORIGINAL

Contains No CBI

Subject: Section 8(e) Submission

Dear Sir or Madam:

This submission is provided on behalf of CONDEA Vista Company (CONDEA Vista) in accordance with section 8(e) of the Toxic Substances Control Act. It presents the results of a developmental toxicity study conducted on 1,2-benzenedicarboxylic acid, di-C_{6-10}- alkyl esters (CAS No. 68515-51-5) refered to in the report as WITAMOL 110/LINPLAST 610P. The details of this study and its findings are provided in the enclosed draft report.

1,2-benzenedicarboxylic acid, di-C_{6-10}-alkyl esters was administered orally by gavage to mated female Sprague-Dawley rats which had been divided into four treatment groups each containing 25 animals. These animals were dosed over days 6-16 of gestation at dose levels of 0, 100, 500 and 100 mg/kg of the test material The animals were killed on Day 20 of gestation and the conceptuses were evaluated. The live fetuses were subsequently examined for developmental abnormalities and variants of the viscera and skeleton, including the state of ossification.

At 1000 mg/kg/day, there was slight increase in weight gain over Days 6-17, principally between Days 13 and 17. Food consumption at this level was also slightly increased. Mean fetal weight and the incidences of embryo-fetal deaths were similar in all groups.

The incidences of fetuses with 14th ribs were increased at 500 and 1000 mg/kg/day; at 1000 mg/kg/day, the incidence of fetuses with retarded sternebrae was also increased. The incidences of the other fetal abnormalities and variants were essentially similar in all groups.

No major developmental effects were observed at any dose level. When administered at 500 mg/kg/day, 1,2-benzenedicarboxylic acid, di-C_{6-10}- alkyl esters produced only minor fetal effects. The 1000 mg/kg/day dose level was associated with only minor maternal and minor fetal effects. The no-observed-effect-level (NOEL) for this study is considered to be 100 mg/kg/day.

This study was co-sponsored by Hüls Aktiengesellschaft and CONDEA Chemie GmbH. Both CONDEA Chemie and CONDEA Vista are wholly-owned subsidiaries of RWE-DEA. CONDEA Vista manufacturers Vista 610P PLASTICIZER, which is similar in composition to 1,2-

benzenedicarboxylic acid, di-C_{6-10}- alkyl esters, at only one site in the U.S. The Vista 610P PLASTICIZER that CONDEA Vista produces never leaves the site where it is produced before it is used, as a plasticizer, in the manufacture of polyvinylchloride compounds.

Under normal manufacturing and compounding conditions there is little or no potential for employee exposure to The Vista 610P PLASTICIZER. In the event of anticipated exposures, recommended protective procedures include the use of chemical goggles and wearing full protective clothing, including boots and gloves. Mechanical ventilation is also recommended if handling the material in enclosed spaces or at elevated temperatures. In cases where additional respiratory protection is required, it is recommended workers use NIOSH-approved organic vapor air-purifying respirators, self-contained breathing apparatus, or air-supplied respirators.

Incorporation of Vista 610P PLASTICIZER into the plastic matrix limits its potential for significant human exposure in down stream applications, such as PVC pipe. The low aqueous solubility of long-chain phthalate esters indicates a low potential for humans to be exposed to significant levels of Vista 610P PLASTICIZER in drinking water. This property would also impede its ability to leach from waste disposal sites.

Based on the protective procedures that CONDEA Vista has in place, the physical/chemical properties of CONDEA Vista 610P PLASTICIZER, and the fact that it is usually encased in a plastic matrix during use, we do not believe that this study provides any reason for a significant health concern associated with its continued manufacture and use. Indeed, the results of this study confirm the absence of any significant developmental toxicity hazard for Vista 610P PLASTICIZER under anticipated manufacturing and use conditions.

Any questions about this submission should be directed to the undersigned as indicated.

Respectfully submitted,

Dave Penney

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IRI Report No. 11520

WITAMOL 110/LINPLAST 610 P
DEVELOPMENTAL TOXICITY STUDY IN RATS

IRI Project No. 491378

IRI

INVERESK RESEARCH INTERNATIONAL LIMITED

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CONFIDENTIAL

Inveresk Research International
Report No. 11520

WITAMOL 110/LINPLAST 610 P
DEVELOPMENTAL TOXICITY STUDY IN RATS

IRI Project No. 491378

Sponsor:

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Total Number of Pages: 62

AUTHENTICATION

'I, the undersigned, hereby declare that this work was performed under my direction and in accordance with the principles of Good Laboratory Practice. The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained.'

S J Barton BA MSc DABT
Study Director

Date:

DRAFT REPORT No. 11520

On receipt of approval or amendments, or 16 weeks from today's date if no amendments have been requested, IRI reserves the right to despatch the final report.

IRI reserves the right to make additional charges for a review of data, amendments or for corrections of minor errors following issue of the final report.

For the final report, this page will be replaced by the Quality Assurance Statement.

Inveresk Research International Limited

ISSUED

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CONTENTS (continued)

PERSONNEL INVOLVED IN PROJECT 491378

Study Director:	S J Barton BA MSc DABT
Project Leader:	S Clubb BSc
Animal Services Manager:	A Dick FIAT
Senior Animal Technician:	F Simpson
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Quality Assurance:	J Wood BSc FIBMS G Cow BSc

SUMMARY

The test material was Witamol 110/Linplast 610 P was received from Hüls AG, Marl, Germany for use in developmental toxicity testing in rats.

Mated female Sprague-Dawley rats were randomised into 4 treatment groups, each containing 25 animals. These animals were dosed orally by gavage over Days 6-16 inclusive of gestation (where Day 0 was the day of detection of mating). Dose levels of test material were as follows:

	$mg.kg^{-1}.day^{-1}$
Control	0
Low dose	100
Intermediate dose	500
High dose	1000

The animals were monitored during gestation for clinical signs of toxicity and for body weight and food consumption performance. They were killed on Day 20 of gestation and the conceptuses were evaluated. The live foetuses were subsequently examined for developmental abnormalities and variants of the viscera and skeleton, including the state of ossification.

At 1000 mg 610 $P.kg^{-1}.day^{-1}$, there was a slight increase in weight gain over Days 6-17, principally between Days 13 and 17. Food consumption at this level was also slightly increased.

Mean foetal weight and the incidences of embryo-foetal deaths were similar in all groups.

The incidences of foetuses with 14th ribs were increased at 500 and 1000 mg 610 P.kg^{-1}.day^{-1}; at 1000 mg 610 P.kg^{-1}.day^{-1}, the incidence of foetuses with retarded sternebrae was also increased.

The incidences of the other foetal abnormalities and variants were essentially similar in all groups.

Under the conditions of this study, 100 mg 610 P.kg^{-1}.day^{-1} was indicated as a level that was without maternal or foetal effects. Dosing at 500 mg 610 P.kg^{-1}.day^{-1} produced only minor foetal effects, and dosing at 1000 mg 610 P.kg^{-1}.day^{-1} was associated with minor maternal and minor foetal effects.

INTRODUCTION

The test material Witamol 110/Linplast 610 P was received from Hüls AG, D-45764 Marl, Germany for use in a developmental toxicity study. This report describes the methods used and the results obtained in the study, which was carried out at Elphinstone Research Centre of Inveresk Research International Limited (IRI) according to the following schedule:

Protocol Signed by Study Director:	7 August 1995
Animal Arrival:	20 October 1995
First Day of Treatment:	23 October 1995
Terminal Necropsies:	6-8 November 1995
Study Completion Date:	See Authentication page for date of Study Director's signature

This developmental toxicity study in rats is part of a programme of experiments designed to evaluate the toxicity of the test material to reproduction in experimental animals.

The rat is a standard rodent species for the developmental toxicity testing in animals required by the Regulatory Authorities. The normal processes of gestation in the rat and the specific background foetal pathology are well documented in this laboratory.

The test material was administered orally by gavage because this is a route of possible exposure in man. Dosing was performed once daily at approximately the same time each day.

All data generated and recorded during this study, including a copy of the final report, will be stored in the Scientific Archives of Inveresk Research International Limited for 5 years after issue of the final report. At the end of the 5 year period the Sponsor will be consulted regarding the disposal or continued storage of raw data.

EXPERIMENTAL PROCEDURE

Test Material

A delivery of 20 litre of Witamol/110/Linplast 610 P, Batch No. 950608 was received at IRI on 2 August 1995. The test material, a colourless liquid was stored in the dark at ambient temperature in the IRI Dispensary. For reporting purposes, the test material will be referred to as 610 P. A copy of the certificate of analysis is reproduced in Appendix 1.

Animals

One batch of 104 time-mated female Sprague-Dawley rats of the Charles River CD strain was ordered from Charles River (UK) Limited, Margate, Kent, England to provide 100 for the study. The delivery, on the 20 October 1995, consisted of 3 sub-batches (32, 36, 36), mated over 3 successive days. On delivery, one batch was on Day 1 of gestation, a second batch on Day 2 and a third on Day 3 of gestation (Day of Mating = Day 0 of gestation). In addition, 5 extra females were delivered. These animals were *ca* 9 weeks of age and weighed *ca* 210 g on arrival.

No more than 2 study females were inseminated by the same male, but the identity of the males was not indicated.

All animals were clinically examined on arrival for signs of abnormality or disease. No such signs were found and the animals were accepted for use in study.

The females were acclimatised in the IRI animal room for 3-5 days prior to dosing.

The 9 animals that were not allocated to treatment groups were not regarded as part of the study.

Animal Management

Room Environment and Sanitation

The study was conducted in the rodent toxicology accommodation (Room L40) of Inveresk Research International Limited.

There was automatic control of light cycle, temperature and humidity. Light hours were 0700-1900 h. Target ranges for temperature and relative humidity were 20°C ± 2°C and 50% ± 15%, respectively, with 15-20 air changes per hour. Daily monitoring of temperature and humidity indicated only occasional minor departures from the temperature target range, none of which were considered to have affected the outcome of the study.

Each day, on completion of all other work, the floor was swept and then mopped with a 0.5% solution of Tego 2000 (Th Goldschmidt Limited, Victoria Road, Ruislip, Middlesex, UK), an amphoteric biocide/cleanser. The room was washed with this solution once weekly.

Caging and Cage Sanitation

The females were housed singly in polypropylene cages with stainless steel grid bottoms and mesh tops, measuring 42 x 27 x 20 cm. A separate stainless steel food hopper and a polycarbonate water bottle were provided for each cage.

Excreta were collected on a tray, lined with absorbent paper, suspended beneath each cage. The cages were suspended on racks containing 6 row of 4 cages.

Cages, tray papers and water bottles were regularly changed as required.

Food and Water

Rat and Mouse Breeder Diet No. 3 (Expanded) SQC was supplied by Special Diets Services (SDS) Limited, Stepfield, Witham, Essex, UK, and was available to the rats *ad libitum*. The food was supplied with batch analyses for nutritive constituents and a range of significant contaminants. A typical analysis, of a batch used during the study, is reproduced in Appendix 2.

The animals had access to domestic mains water *ad libitum*. The supply is analysed regularly for dissolved and suspended materials, including a range of significant contaminants. The results of a typical, recent analysis are reproduced in Appendix 3.

None of the contaminants revealed by the analyses of food and water were considered to have been present in sufficient quantity to have affected the outcome of the study.

Allocation of Animals to Treatment Groups

Each female was allocated on arrival to a treatment group using a computer generated series of randomly sequenced numbers. Cages in any one treatment group were evenly distributed throughout the caging system.

Each animal received a subcutaneously implanted electronic identification chip which identified it individually within the study and which corresponded to that animal's number. Where the subcutaneously implanted electronic chip failed to function the affected animal had a replacement chip implanted.

Each animal was ascribed a cage card which was colour coded for treatment group and marked with the project, cage and animal numbers, sex and the relevant treatment.

The treatment groups and animal numbers were arranged as follows:

Group No.	Treatment and Dose Level (mg 610 P.kg^{-1}.day^{-1})		Animal Nos.
1	Control	0	1-25
2	Low dose	100	26-50
3	Intermediate dose	500	51-75
4	High dose	1000	76-100

Selection of Dose Levels

Dose levels were agreed with the Sponsor, based on data available to the Sponsor.

Treatment Regime

The animals were dosed orally by gavage at a dose volume of 5 ml per kg of body weight. The volume of solution to be administered to each animal was determined each day by the weight of that animal as measured at the time of administration.

All animals were dosed once daily at approximately the same time each day, over Days 6-16 inclusive of gestation.

Preparation of Dosing Solutions

The dosing solutions were prepared fresh daily for the first 5 days of the dosing period. For the remaining 8 days of dosing, a single batch was prepared for each level, and a suitable aliquot from each batch was dispensed daily to the animal room. Stability over 8 days has been demonstrated (IRI Project 373865).

The dosing solutions were prepared by weighing the requisite quantity of test material into a glass container and adding the correct quantity of vehicle (maize oil). The solutions were mixed by gentle manual inversion.

The Control animals received the vehicle.

Analysis of Dosing Solutions

Triplicate samples were taken from all dosing solutions on 2 occasions, the first and fifth days of the dosing period. These samples were analysed for concentration and homogeneity in the IRI Analytical Chemistry Laboratory by Method No. 7386 developed under the provisions of IRI Project No. 373865.

Observations

Clinical Observations

All the animals were examined for general condition and reaction to treatment on each day. The onset, duration and intensity of any signs were recorded, with particular attention being paid to the period 1-2 h after dosing.

All the animals were checked for viability at the beginning of each day, and again as late as practical on each day.

Body Weight

Weights were recorded on Days 4, 6-17 and 20 of gestation, but for clarity/brevity of reporting, only the weights on Days 4, 6, 9, 13, 17 and 20 are presented in this report, although all weights are being retained in the archive.

Food Consumption

The weight of food consumed by each animal was recorded daily commencing on Day 3 of gestation (weighed quantity offered on Day 3, residue recorded on Day 4).

Terminal Studies

The adult animals were killed by exposure to carbon dioxide. Foetuses were killed by chilling at *ca* 4°C for at least 5 min prior to fixation.

Each dam was subjected to a gross necropsy in which the thoracic and abdominal contents were examined macroscopically, and any findings were recorded.

The reproductive tract was dissected out and weighed intact, and the maternal carcass was discarded. The uterus was then opened and the contents were examined. The number of *corpora lutea graviditatis* in each ovary and the number and position of all implantation sites in the uterus were recorded, each implant being classified as either live, a foetal death (death judged to have occurred from *ca* Day 16 of gestation), a late embryonic death (embryonic remains visible), or an early embryonic death (only early placental remains or a decidual scar visible).

Each live foetus was individually identified within the litter and its weight was recorded. The foetuses were examined for externally visible abnormalities, then approximately one half of the foetuses from each uterus were fixed in methylated ethyl alcohol, the remaining half in Bouin's fluid.

The foetuses fixed in alcohol were subsequently examined by open dissection for the occurrence of gross visceral abnormalities. The eviscerated carcasses were then macerated in potassium hydroxide, the skeletons stained with Alizarin Red S, then the

foetuses were cleared with aqueous glycerol solutions. Skeletal structures in these preparations were examined for abnormalities and variants, including state of ossification.

The foetuses fixed in Bouin's fluid were examined for visceral abnormalities by a freehand serial sectioning technique derived from that of Wilson (1965).

The sex of each foetus was determined during visceral examination.

Statistical Analysis of Results

Body weight gains from Day 6 of gestation were generally analysed by parametric analysis of variance (Snedecor and Cochran, 1980). Pairwise comparisons between each treatment level and Control were performed using Dunnett's test (Dunnett, 1964). Where there was significant heterogeneity of variance, a log or square root transformation was used in an attempt to stabilise the variances. Where transformation failed to stabilise the variances, the Kruskal-Wallis test was used instead (Hollander and Wolfe, 1973).

For other parameters, it was not considered useful to conduct formal statistical analysis. Interpretation was based on inspection of the individual and group values.

RESULTS

Analysis of Dosing Solutions (Appendix 4)

The analysed concentrations of all the dosing solutions were within ± 10% of the nominal, indicating satisfactory accuracy of formulation. The low coefficients of variation indicated satisfactory homogeneity.

Clinical Observations and Necropsy Findings (Table 1, Appendix 5)

At 1000 mg 610 $P.kg^{-1}.day^{-1}$, there was a slight increase in the incidence of piloerection.

There were no other clinical observations or necropsy findings that were considered to have been associated with treatment.

Body Weight Performance (Table 2, Appendix 6)

At 1000 mg 610 $P.kg^{-1}.day^{-1}$, there was a slight increase in weight gain over Days 6-17, principally between Days 13 and 17, with the increase over Days 6-17 just failing to achieve statistical significant ($P > 0.05$).

At 100 and 500 mg 610 $P.kg^{-1}.day^{-1}$, mean weight gains were marginally greater than Control, but the differences were considered too small to be attributed to treatment.

Food Consumption (Table 3, Appendix 7)

At 1000 mg 610 $P.kg^{-1}.day^{-1}$, there was a slight increase in food consumption from Day 10 of gestation.

At 500 and 100 mg 610 P.kg^{-1}.day^{-1}, food consumption was essentially similar to that of the Controls.

Pregnancy Performance and Foetal Weight (Table 4, Appendix 8)

The pregnancy frequencies at 100 and 1000 mg 610 P.kg^{-1}.day^{-1} were lower than those of the Controls or at 500 mg 610 P.kg^{-1}.day^{-1}. However, events leading to the establishment of pregnancy should have occurred prior to commencement of treatment, and therefore the lower pregnancy frequencies at 100 and 1000 mg 610 P.kg^{-1}.day^{-1} were considered to be incidental.

There were no indications of an effect of treatment on the frequency of embryo-foetal deaths or on foetal weight.

Foetal Abnormalities and Variants (Tables 5-7, Appendices 9-11)

The incidence of major abnormalities did not indicate an effect of treatment. All of the abnormalities seen at 1000 mg 610 P.kg^{-1}.day^{-1} have been seen previously in this laboratory.

The incidence of minor visceral abnormalities was similar in all groups.

The incidences of foetuses with 14th ribs were increased at 500 and 1000 mg 610 P.kg^{-1}.day^{-1}; the incidence at 100 mg 610 P.kg^{-1}.day^{-1} was similar to Control. At 1000 mg 610 P.kg^{-1}.day^{-1}; the incidence of foetuses with retarded sternebrae was increased compared with Control. At 100 and 500 mg 610 P.kg^{-1}.day^{-1}, the incidences of retarded sternebrae were not noticeably different from Control.

The incidences of the other skeletal abnormalities and variants, including the other ossification parameters, were essentially similar in all groups.

DISCUSSION AND CONCLUSION

At 1000 mg 610 P.kg^{-1}.day^{-1} there were slight maternal effects, indicated by slightly increased body weight gain and food consumption. There were no indications of maternal effects at the lower levels.

Foetal effects were confined to increases in the incidences of supernumerary ribs (but only classed as vestigial) at 500 and 1000 mg 610 P.kg^{-1}.day^{-1}, and to a slight increase in the incidence of retarded sternebrae at 1000 mg 610 P.kg^{-1}.day^{-1}. Both of these findings were considered to be of a minor nature.

Under the conditions of this study, 100 mg 610 P.kg^{-1}.day^{-1} was indicated as a level that was without maternal or foetal effects. Dosing at 500 mg 610 P.kg^{-1}.day^{-1} produced only minor foetal effects, and dosing at 1000 mg 610 P.kg^{-1}.day^{-1} was associated with minor maternal and minor foetal effects.

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Snedecor, G W and Cochran, W G (1980). Statistical Methods, 7th Edition, 213-254 and 365-392, Iowa State University Press.

Wilson, T G (1965). Teratology: Principles and Techniques, Wilson J G and Warkony J, Eds, 267-277. The University of Chicago Press, Chicago, Illinois.

TABLE 1

610 P
Developmental Toxicity Study in Rats
Group Incidence of Clinical Observations and Necropsy Findings

Observation/Finding	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (500)	4 (1000)
Brown staining nasal region	1	1	0	2
Lower teeth cut; upper teeth broken	0	1	0	0
Wet/ stained vagina	0	0	1	1
Soft faeces	0	0	0	1
Lump upper caudal region	1	0	0	0
Scabbing	1	1	0	0
Unkempt coat	0	0	1	0
Hairloss	0	0	0	1
Piloerection	0	1	2	5
Aggressive/ agitated behaviour	0	0	1	1
Irregular respiration	0	0	0	1
Thin	0	1	0	0
Connected spleen and left kidney	1	0	0	0
Distended uterine horn	0	0	1	0

TABLE 2

610 P
Developmental Toxicity Study in Rats
Group Mean Body Weight (g) ± Standard Deviation
(Pregnant Animals Only)

Day of Gestation	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (500)	4 (1000)
4	225 ± 10	227 ± 11	224 ± 11	230 ± 8
6	242 ± 9	243 ± 9	241 ± 13	247 ± 9
9	259 ± 11	262 ± 10	260 ± 15	263 ± 9
13	294 ± 13	297 ± 12	295 ± 18	299 ± 11
17	335 ± 16	342 ± 13	341 ± 28	348 ± 14
20	386 ± 24	394 ± 19	389 ± 36	397 ± 18
Gain Days 6-17	93 ± 11	99 ± 10	99 ± 19	102 ± 8
% of Control	-	106	106	110

Means are based on 17-25 animals

TABLE 3

610 P
Developmental Toxicity Study in Rats
Group Mean Food Consumption (g) ± Standard Deviation
(Pregnant Animals Only)

Day of Gestation	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (500)	4 (1000)
3	28	28	28	28
4	26	27	25	27
5	28	28	28	29
6	25	24	25	26
7	28	28	29	29
8	28	28	29	29
9	30	29	30	31
10	30	32	32	33
11	32	32	32	35
12	31	32	32	34
13	31	31	31	34
14	33	33	34	36
15	35	35	34	36
16	34	34	35	36
17	38	37	36	39
18	34	36	35	37
19	28	29	29	31
Total Mean Consumed Days 6-16	337	338	343	359
% of Control	-	100	102	107

Means are based on 17-25 animals

TABLE 4

610 P
Developmental Toxicity Study in Rats
Pregnancy Performance and Foetal Weight

	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (500)	4 (1000)
Number of animals mated	25	25	25	25
Number pregnant at Day 20 necropsy	25	17	23	19
Pregnancy frequency as %	100	68	92	76
Total corpora lutea graviditatis	355	232[a]	309	258
Total number of implants	327	232 (218[a])	284	243
Pre-implantation loss as %	8	6[a]	8	6
Total live implants (%)	307 (94)	218 (94)	267 (94)	227 (93)
Total dead implants (%)	20 (6)	14 (6)	17 (6)	16 (7)
Total early embryonic deaths (%)	18 (6)	12 (5)	15 (5)	13 (5)
Total late embryonic deaths (%)	1 (0.3)	2 (1)	2 (1)	3 (1)
Total foetal deaths (%)	1 (0.3)	0	0	0
Mean corpora lutea graviditatis	14.2 ± 1.9	14.5 ± 1.4	13.4 ± 3.0	13.6 ± 1.9
Mean implants	13.1 ± 2.2	13.6 ± 1.8	12.3 ± 3.5	12.8 ± 1.3
Mean live implants	12.3 ± 2.7	12.8 ± 1.7	11.6 ± 3.3	11.9 ± 2.2
Mean dead implants	0.8 ± 1.3	0.8 ± 0.7	0.7 ± 1.0	0.8 ± 1.3
Mean early embryonic deaths	0.7 ± 1.3	0.7 ± 0.8	0.7 ± 0.8	0.7 ± 1.2
Mean late embryonic deaths	0.04 ± 0.2	0.1 ± 0.3	0.1 ± 0.3	0.2 ± 0.4
Mean foetal deaths	0.04 ± 0.2	0	0	0
Total live male foetuses (%)	154 (50)	119 (55)	148 (55)	107 (47)
Total live female foetuses (%)	153 (50)	99 (45)	119 (45)	120 (53)
Live foetal sex ratio (♂:♀)	1:0.99	1:0.83	1:0.80	1:1.12
Mean total uterus weight (g)	78 ± 16	83 ± 10	77 ± 21	78 ± 11
Mean litter mean foetal weight (g)	4.04 ± 0.27	4.10 ± 0.19	4.09 ± 0.36	4.04 ± 0.34

Means are given ± Standard Deviation
a = Values excluded Animal 33

TABLE 5

610 P
Developmental Toxicity Study in Rats
Group Incidence of Major Foetal Abnormalities

Abnormality	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (500)	4 (1000)
	Incidence of Foetuses (Litters)			
Hunched posture with distorted clavicles and ribcage; flexure of forelimbs	1 (1)	0	0	2 (1)
Left microphthalmia	0	0	1 (1)	0
Retro-oesophageal right subclavian artery	0	0	0	1 (1)
Interventricular septal defects	0	0	0	1 (1)
Dilated ductus arteriosus; pulmonary trunk and ascending aorta appears to arise from right ventricle; interventricular septal defect	0	0	0	1 (1)
Distorted ribs	0	0	1 (1)	0
Craniofacial abnormalities, cervical oedema, malrotated hindlimbs	0	0	1 (1)	0
Number with major abnormality	1 (1)	0	3 (3)	5 (2)
Total number examined	307 (25)	218 (17)	267 (23)	227 (19)

TABLE 6

610 P
Developmental Toxicity Study in Rats
Group Incidence of Minor Foetal Abnormalities and Variants

Abnormality/Variant	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (500)	4 (1000)
	Incidence of Foetuses (Litters)			
Visceral				
Haemorrhage affecting:				
Head	1 (1)	2 (2)	1 (1)	1 (1)
Trunk	0	2 (2)	3 (3)	0
Limbs	0	0	3 (3)	0
Subdural haemorrhage brain	1 (1)	0	1 (1)	0
Small eye	0	0	1 (1)	0
Small thyroid	0	0	0	1 (1)
Interventricular septal defect (small)	0	1 (1)	0	0
Absent innominate artery	0	0	0	1 (1)
Enlarged left ventricle	0	0	0	1 (1)
Abnormal lobation of liver	1 (1)	1 (1)	1 (1)	1 (1)
Hepatic haemorrhage	1 (1)	3 (2)	2 (2)	1 (1)
Intra-abdominal haemorrhage	2 (2)	3 (1)	2 (2)	2 (1)
Thin diaphragm and/or protrusion of median liver lobe	1 (1)	0	0	2 (2)
Increased renal pelvic cavitation	1 (1)	0	1 (1)	0
Dilated ureter(s)	8 (7)	1 (1)	1 (1)	2 (2)
Testis(es) not fully descended to pelvic position	0	1 (1)	1 (1)	1 (1)
Medial displacement of testis	0	1 (1)	0	0
Number with minor visceral abnormality/variant	15 (11)	13 (7)	17 (11)	13 (8)
Number examined by Wilson sectioning	153 (25)	109 (17)	133 (22)	114 (19)
Total number examined viscerally	307 (25)	218 (17)	266 (22)	227 (19)

TABLE 6 (continued)

Group Incidence of Minor Foetal Abnormalities and Variants

Abnormality/Variant	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (500)	4 (1000)
	Incidence of Foetuses (Litters)			
Skeletal				
Sutural bone	1 (1)	2 (2)	1 (1)	1 (1)
Cervical rib(s)	0	3 (3)	1 (1)	4 (3)
Minimal distortion of rib(s)	0	1 (1)	1 (1)	1 (1)
Misshapen 6th sternebra	1 (1)	1 (1)	1 (1)	0
Asymmetric pelvic girdle	0	0	0	1 (1)
Number of ribs:				
Reduced 13th rib	0	0	0	1 (1)
13 complete rib(s)	142 (25)	95 (17)	97 (22)	57 (17)
14th vestigial supernumerary rib(s)	12 (9)	14 (8)	37 (15)	55 (15)
Number with minor skeletal abnormality/variant	2 (2)	5 (5)	4 (4)	7 (5)
Total number examined skeletally	154 (25)	109 (17)	134 (22)	113 (19)

TABLE 7

610 P
Developmental Toxicity Study in Rats
Group Incidence of Incomplete Ossification Parameters

Parameter	Group/Dose Level (mg 610 P.kg^{-1}.day^{-1})			
	1 (0)	2 (100)	3 (300)	4 (1000)
	Incidence of Foetuses (litters)			
Incomplete ossification affecting:				
≤3 skull bones	14 (8)	8 (6)	21 (11)	20 (11)
≥4 skull bones	3 (3)	1 (1)	5 (5)	4 (2)
Thoracic vertebral centrum(a)	4 (3)	6 (4)	3 (2)	4 (3)
2nd and 4th metacarpal(s)	1 (1)	0	0	1 (1)
Pubis(es)	1 (1)	1 (1)	0	1 (1)
Ischium	1 (1)	0	0	1 (1)
Cervical vertebral arch(es)	0	0	1 (1)	0
Lumbar vertebral centrum (a)	0	0	0	1 (1)
Sacral vertebral arch(es)	12 (8)	5 (3)	3 (2)	2 (2)
2nd to 4th metatarsal	0	0	1 (1)	0
Unossified 5th metacarpal(s)/metatarsal(s)	30 (16)	26 (11)	17 (7)	32 (14)
Number of sternebrae retarded:				
0	103 (24)	72 (16)	70 (18)	35 (15)
1	33 (16)	29 (11)	42 (16)	51 (17)
2	17 (9)	8 (5)	20 (9)	20 (11)
3	1 (1)	0	0	2 (1)
>3	0	0	1 (1)	4 (2)
Total number examined	154 (25)	109 (17)	134 (23)	113 (19)

APPENDIX 1

610 P

Developmental Toxicity Study in Rats

Certificate of Analysis of Test Material

APPENDIX 2

610 P

Developmental Toxicity Study in Rats

Analysis of Diet

SDS
SPECIAL DIETS SERVICES

Special Quality Control
Certificate of Analysis

PRODUCT: RM3 (E) SQC
BATCH NO: 1792 PREMIX BATCH NO: 972
DATE OF MANUFACTURE: 27-JUL-95

Nutrient	Found Analysis		Contaminant	Found Analysis		Limit of Detection
Moisture	8.9	%	Fluoride	48	mg/kg	1.0 mg/kg
Crude Fat	5.1	%	Nitrate as NaNO3	54	mg/kg	1.0 mg/kg
Crude Protein	23.1	%	Nitrite as NaNO2	Non Detected	mg/kg	1.0 mg/kg
Crude Fibre	4.4	%	Lead	0.80	mg/kg	0.25 mg/kg
Ash	6.7	%	Arsenic	0.21	mg/kg	0.2 mg/kg
Calcium	1.25	%	Cadmium	0.07	mg/kg	0.05 mg/kg
Phosphorus	0.81	%	Mercury	Non Detected	mg/kg	0.01 mg/kg
Sodium	0.41	%	Selenium	0.15	mg/kg	0.05 mg/kg
Chloride	0.72	%				
Potassium	1.03	%				
Magnesium	0.23	%	Total Aflatoxins	Non Detected	mcg/kg	1 mcg/kg each of B1,B2,G1,G2
Iron	262	mg/kg				
Copper	14	mg/kg	Total P.C.B	Non Detected	mcg/kg	10.0 mcg/kg
Manganese	74	mg/kg	Total D.D.T	Non Detected	mcg/kg	1.0 mcg/kg
Zinc	66	mg/kg	Dieldrin	Non Detected	mcg/kg	1.0 mcg/kg
			Lindane	2	mcg/kg	1.0 mcg/kg
			Heptachlor	Non Detected	mcg/kg	1.0 mcg/kg
			Malathion	58	mcg/kg	20.0 mcg/kg
Vitamin A	12.4	iu/g	Total Viable Organisms x 1000	Non Detected	per grm	1000/g
Vitamin E	77	mg/kg				
Vitamin C		mg/kg	Mesophilic Spores x 100	3.75	per grm	100/g
			Salmonellae Species	Non Detected	per grm	Absent in 20 grm
			Presumptive E.coli	Non Detected	per grm	Absent in 20 grm
			E.coli Type 1	Non Detected	per grm	Absent in 20 grm
			Fungal Units	125	per grm	Absent in 20 grm
			Antibiotic Activity	Non Detected		

Signed R S Flud
Dated 23/8/95

APPENDIX 3

610 P

Developmental Toxicity Study in Rats

Analysis of Water

LOTHIAN REGIONAL COUNCIL

WATER AND DRAINAGE

Water Quality Division

4 Marine Esplanade, Edinburgh, EH6 7LU

Tel: 0131 553 8212
Fax: 0131 553 5804

TEST REPORT

Inveresk Research Int. Ltd.
Environmental Chemistry
Tranent
EH33 2NE

F.A.O.: Alison Barclay

Date of Report	14/03/96
Order No.:	None.
Lab. Ref.:	WM/11968
Cust. Ref.:	None.
Taken on:	06/02/96
Received on:	06/02/96
Taken by:	A. Barclay.
Analysis Started:	07/02/96
Page:	1 of 2

Description: IRI, Block C Water.

Test Results:

pH	8.2	*Manganese (as Mn)*	*1.0 ug/l*
Suspended solids	*1 mg/l*	*Coliform organisms*	*0 /100ml*
Chloride (as Cl)	*11 mg/l*	*E.coli*	*0 /100ml*
Fluoride (as F)	*<100 ug/l*	*Plate count at 22C*	*0 /ml*
Nitrate (as NO3)	*3.85 mg/l*	*Plate count at 37C*	*0 /ml*
Sulphate (as SO4)	*18 mg/l*	*Salmonella spp.*	*Absent*
Alkalinity (as HCO3)	*51 mg/l*	*Volume filtered*	*1 litres*
Conductivity	*156 uS/cm*	*C.Perf*	*53 /100ml*
Silver (as Ag)	*<0.18 ug/l*	*F.Strep*	*0 /100ml*
Aluminium (as Al)	*26 ug/l*	*Ammonia (as NH4)*	*<0.02 mg/L*
Arsenic (as As)	*<5 ug/l*	*Nickel (as Ni)*	*<15 ug/l*
Boron (as B)	*<17 ug/l*	*Nitrite (as NO2)*	*<0.01 mg/l*
Barium (as Ba)	*19.2 ug/l*	*Heptachlor*	*<0.010 ug/l*
Cadmium (as Cd)	*<0.14 ug/L*	*Trifluralin*	*<0.010 ug/l*
COD	*<30 mg/l*	*alpha endosulphan*	*<0.010 ug/l*
Chromium (as Cr)	*<1.7 ug/l*	*beta endosulphan*	*<0.010 ug/l*
Copper (as Cu)	*6.5 ug/l*	*isodrin*	*<0.010 ug/l*
Dry Residues	*113 mg/l*	*opDDE*	*<0.010 ug/l*
Iron (as Fe)	*30 ug/l*	*opDDT*	*<0.010 ug/l*
Total Haloforms	*9 ug/l*	*opTDE*	*<0.010 ug/l*
bromodichloromethane	*3.1 ug/l*	*Aldrin*	*<0.010 ug/l*
bromoform	*<2.0 ug/l*	*Alpha HCH*	*<0.010 ug/l*
chloroform	*6.0 ug/l*	*Dieldrin*	*<0.010 ug/l*
dibromochloromethane	*<2.0 ug/l*	*Endrin*	*<0.010 ug/l*
Calcium (as Ca)	*15.3 mg/l*	*Gamma HCH*	*<0.010 ug/l*
Magnesium (as Mg)	*6.2 mg/l*	*HCB*	*<0.010 ug/l*
Total Hardness (as Ca)	*26 mg/l*	*ppDDE*	*<0.010 ug/l*
Mercury (as Hg)	*<0.05 ug/l*	*ppDDT*	*<0.010 ug/l*
Potassium (as K)	*0.62 mg/l*	*ppTDE*	*<0.010 ug/l*
Sodium (as Na)	*6.5 mg/l*	*Carbophenothion*	*<0.010 ug/l*

Signature: [signature] *Date:* 17/3/96

C HALL
SENIOR CHEMIST

APPENDIX 3 (continued)

Lab. Ref.: WM/11958

Ethyl parathion	<0.010 ug/l	*TOTAL*	0.000 ugs/l
Fenthion	<0.010 ug/l	*2,4,6 Tri Chlorophenol*	<0.05 ug/l
Methyl parathion	<0.010 ug/l	*Pentachlorophenol*	<0.05 ug/l
Azinphos ethyl	<0.010 ug/l	*Phenol*	<0.05 ug/l
Fenitrothion	<0.010 ug/l	*Total Cresols (m,p,o)*	<0.15 ug/l
Malathion	<0.010 ug/l	*Total Phenols*	<0.05 ug/l
Methyl azinphos	<0.010 ug/l	*m Chlorophenol*	<0.05 ug/l
Benzo(a)pyrene	<0.001 ug/l	*o Chlorophenol*	<0.05 ug/l
Benzo(b)fluoranthene	<0.004 ug/l	*Phosphorus SR (as P)*	<65 ug/l
Benzo(ghi)perylene	<0.004 ug/l	*Oxidizability (as O)*	0.54 mg/l
Benzo(k)fluoranthene	<0.004 ug/l	*Selenium (as Se)*	<1 ug/L
Fluoranthene	0.007 ug/l	*Sulphide (as S)*	<0.1 mg/l
Indeno(123cd)pyrene	<0.004 ug/l	*Total Organic Carbon (as C)*	1.3 mg/l
Total PAHs	0.013 ug/l	*Atrazine*	<0.010 ug/l
Lead (as Pb)	<0.8 ug/l	*Propazine*	<0.010 ug/l
CB 101	<0.010 ugs/l	*Simazine*	<0.010 ug/l
CB 105	<0.010 ugs/l	*Tnetazine*	<0.010 ug/l
CB 118	<0.010 ugs/l	*Turbidity*	0.16 NTU
CB 138	<0.010 ugs/l	*1,2 dichloroethane*	<1.0 ug/l
CB 149	<0.010 ugs/l	*1,2,4 trichlorobenzene*	<1.0 ug/l
CB 153	<0.010 ugs/l	*3-chlorotoluene*	<1.0 ug/l
CB 180	<0.010 ugs/l	*Tetrachloroethene*	<1.0 ug/l
CB 28	<0.010 ugs/l	*Tetrachloromethane*	<0.3 ug/l
CB 31	<0.010 ugs/l	*Trichloroethene*	<3.0 ug/l
CB 52	<0.010 ugs/l	*Zinc (as Zn)*	2.5 ug/l

Authorisation Notes:

Signature: Date: 11/7/96
C HALL
SENIOR CHEMIST

APPENDIX 4

610 P
Developmental Toxicity Study in Rats
Analysis of Dosing Solutions

Day 1 of dosing

Dose Group	Nominal Concentration ($mg.ml^{-1}$)	Found Concentration ($mg.ml^{-1}$)	Mean Found ($mg.ml^{-1}$)	Coefficient of Variation (%)	% Difference from Nominal
1	0	0 0 0	0	-	-
2	20	22.4 21.8 21.8	22.0	1.6	10.0
3	100	104 101 103	103	1.5	3.0
4	200	208 199 213	207	3.4	3.5

Day 5 of Dosing

Dose Group	Nominal Concentration ($mg.ml^{-1}$)	Found Concentration ($mg.ml^{-1}$)	Mean Found ($mg.ml^{-1}$)	Coefficient of Variation (%)	% Difference from Nominal
1	0	0 0 0	0	-	-
2	20	18.9 19.2 18.8	19.0	1.1	-5.0
3	100	99.3 99.6 98.5	99.1	0.6	-0.9
4	200	202 202 204	203	0.6	1.5

APPENDIX 5

610 P
Developmental Toxicity Study in Rats
Individual Clinical Observations and Necropsy Findings

Group/ Dose Level (mg 610 P. $kg^{-1}.day^{-1}$)	Animal Number	Clinical Observations	Day(s) of Gestation Recorded	Necropsy Findings
1 (0)	11	NAD	-	Spleen connected to left kidney with connective tissue
	15	Lump upper caudal region	7-20	Scabbing caudal region; lump not apparent
	23	Brown staining nasal region	12-15	NAD
2	27	Black scabs dorsal abdomen	16-20	NAD
(100)	36	Thin	14-20	NAD
		Piloerection	13-20	
	41	Brown staining nasal region	13-19	Mild brown staining nasal region
		Lower teeth cut/overgrown	7	
		Upper teeth broken	6-14	
3	54	Piloerection	17-19	NAD
(500)	56	Mild aggressive behaviour	9-18	NAD
		Mild piloerection	17-20	
	59	Wet vagina	19	Left uterine horn distended with watery, red/ brown fluid
	61	Unkempt coat dorsal surface	14-17	NAD
4	81	Irregular respiration	16-20	NAD
(1000)		Agitated behaviour	16-18	
		Piloerection	17-20	
	83	Piloerection	15-19	NAD
	84	Brown staining nasal region	14-16	NAD
	93	Brown staining nasal region	9-10	NAD
		Piloerection	11-20	
	95	Staining around vagina	18,19	Dark staining around vagina
		Soft faeces	19,20	
	96	Piloerection	14-17	NAD
	99	Piloerection	11-18	NAD
	100	Partial hair loss on forelimbs	13-20	Mild hair loss lower forelimbs Hair loss left hindlimb and lower right hindlimb

NAD = No abnormality detected

APPENDIX 6

610 P
Developmental Toxicity Study in Rats
Individual Body Weight Data (g)

Group 1, Control: 0 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Day of Gestation					
	4	6	9	13	17	20
1	233	243	259	292	321	373
2	227	242	257	288	323	380
3	237	254	269	306	356	420
4	231	246	267	298	339	406
5	216	237	255	276	300	332
6	232	249	261	290	339	399
7	228	244	268	299	341	398
8	240	256	271	310	361	421
9	219	234	247	280	318	365
10	228	249	264	301	350	402
11	228	245	263	306	354	416
12	219	233	248	285	327	365
13	229	243	262	297	335	384
14	223	239	256	291	330	379
15	230	243	266	291	338	386
16	204	221	228	268	304	340
17	220	235	254	296	345	378
18	238	252	276	311	348	415
19	238	255	269	312	350	409
20	206	226	245	282	327	380
21	223	243	259	284	331	374
22	212	226	239	266	304	345
23	225	247	275	308	345	397
24	228	249	266	303	341	397
25	214	238	258	301	346	391

APPENDIX 6 (continued)

Individual Body Weight Data (g)

Group 2, Low dose: 100 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Day of Gestation					
	4	6	9	13	17	20
26	237	250	269	308	356	408
27	228	245	274	314	352	409
28	230	243	261	294	332	393
29	236	247	267	307	351	401
30	223	243	266	311	361	430
31	217	230	254	280	328	388
32	224	238	251	290	335	373
33	207	233	250	288	331	377
34	232	248	267	304	343	392
35	225	233	251	283	328	370
(36)	203	214	224	233	239	248
(37)	232	244	264	265	263	272
38	221	238	255	290	342	392
39	229	239	261	292	335	380
(40)	217	228	234	244	258	262
41	243	258	271	314	355	409
(42)	NR	255	268	297	295	305
(43)	231	260	282	284	288	304
44	208	232	248	284	344	405
45	231	250	269	304	343	401
46	222	240	258	281	312	353
(47)	222	232	246	275	289	289
(48)	221	238	265	286	289	296
49	247	264	284	313	360	409
(50)	208	220	235	237	242	258

( ) = Animal not pregnant
NR = Not recorded

APPENDIX 6 (continued)

Individual Body Weight Data (g)

Group 3, Intermediate dose: 500 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Day of Gestation					
	4	6	9	13	17	20
51	232	254	270	303	352	422
52	219	231	243	285	326	376
53	237	258	277	320	367	431
(54)	214	227	231	242	249	267
55	214	225	237	269	301	350
56	224	227	253	276	305	355
57	237	251	267	296	337	391
58	219	243	257	285	341	403
59	218	233	245	274	274	285
60	225	242	253	283	329	374
61	240	251	268	309	368	414
62	215	223	245	274	328	365
63	220	238	257	287	333	371
64	241	255	278	315	371	417
(65)	234	247	261	272	281	285
66	237	259	279	320	387	428
67	NR	247	268	299	352	396
68	224	242	262	297	341	384
69	229	252	271	309	359	411
70	199	214	233	264	307	345
71	239	259	284	326	381	434
72	210	229	242	275	313	356
73	217	234	252	296	349	400
74	212	236	256	300	351	408
75	229	248	275	312	361	423

( ) = Animal not pregnant
NR = Not recorded

APPENDIX 6 (continued)

Individual Body Weight Data (g)

Group 4, High dose: 1000 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Day of Gestation					
	4	6	9	13	17	20
(76)	216	232	242	244	242	256
77	233	241	251	280	329	395
78	248	262	280	320	377	435
79	237	250	267	306	351	413
80	223	237	251	283	326	373
81	217	234	252	293	331	389
82	229	247	252	293	344	393
(83)	204	219	221	232	243	249
84	241	254	273	303	353	391
85	222	236	254	286	341	381
86	230	243	262	292	341	388
87	229	249	268	305	358	404
88	225	235	253	294	338	374
(89)	236	252	267	276	287	295
90	239	260	270	313	368	421
91	221	234	250	289	336	364
92	233	245	269	300	346	407
93	233	259	272	317	360	418
(94)	228	239	250	268	276	290
95	222	245	262	296	345	386
(96)	201	214	219	231	246	244
97	223	250	266	309	354	394
(98)	204	221	233	247	263	275
99	241	259	270	298	353	409
100	223	248	271	311	366	414

( ) = Animal not pregnant

APPENDIX 7

610 P
Developmental Toxicity Study in Rats
Individual Food Consumption Data (g)

Group 1, Control: 0 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Day of Gestation																
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	27	27	31	11	29	25	32	29	34	34	31	34	39	37	39	36	38
2	28	30	27	17	30	26	27	29	33	32	26	32	37	36	37	36	37
3	24	23	29	17	28	25	29	28	36	32	31	33	39	36	43	37	33
4	28	30	24	20	32	31	30	31	31	30	29	33	37	36	43	35	36
5	27	29	30	15	30	30	27	32	33	33	25	33	34	32	37	32	35
6	30	31	27	24	31	24	35	29	35	32	30	33	36	38	38	35	33
7	30	28	24	26	32	30	32	33	37	36	29	38	39	35	45	38	37
8	28	30	33	23	32	27	31	32	35	32	31	34	35	37	40	37	32
9	27	27	19	25	26	~~29~~	26	32	30	26	29	31	30	33	32	36	26
10	29	30	25	31	26	30	30	35	34	29	34	36	32	36	37	38	30
11	28	29	28	32	28	29	32	34	35	31	32	37	40	35	41	33	31
12	28	28	24	29	24	27	30	29	34	29	32	34	35	37	36	31	24
13	24	28	22	26	20	23	25	24	30	28	27	32	32	30	31	39	27
14	28	23	25	28	26	27	29	30	33	31	30	32	33	33	36	36	29
15	31	30	23	32	31	32	31	35	36	29	32	30	34	33	33	35	37
16	23	23	21	25	19	24	22	27	26	27	27	28	30	32	27	29	26
17	30	26	23	28	25	31	29	34	37	31	35	33	37	37	37	40	24
18	29	19	31	25	29	28	32	28	32	31	33	31	33	30	39	30	21
19	28	22	30	25	25	27	29	30	28	32	32	30	35	33	46	32	19
20	26	25	30	24	27	27	30	28	27	31	27	31	31	30	34	29	16
21	24	19	30	24	26	27	28	28	27	29	31	31	32	34	34	35	14
22	26	19	30	21	25	23	27	24	25	27	28	29	28	28	31	30	15
23	33	28	37	29	33	34	37	36	33	34	42	34	37	34	46	38	17
24	25	31	36	31	33	33	34	34	32	34	35	36	38	34	43	27	35
25	28	19	33	26	32	29	33	31	30	32	33	34	34	35	35	32	22

APPENDIX 7 (continued)

Individual Food Consumption Data (g)

Group 2, Low dose: 100 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Day of Gestation																
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
26	28	25	26	18	31	32	30	30	33	34	29	34	37	36	38	36	32
27	29	29	28	23	32	29	29	32	33	36	29	31	36	34	41	34	36
28	28	29	25	20	32	28	28	32	34	31	32	31	34	34	36	36	36
29	30	33	26	13	33	30	32	32	35	36	30	35	39	38	39	40	35
30	31	29	31	15	32	34	32	35	40	37	36	38	45	39	42	46	36
31	26	22	28	17	28	28	28	30	33	29	27	35	33	34	38	34	31
32	24	24	28	20	27	22	25	27	30	30	26	32	32	35	36	34	25
33	22	29	28	23	29	26	28	30	34	33	28	33	39	33	39	34	30
34	24	27	24	29	28	29	30	33	31	29	32	32	33	30	35	33	27
35	29	26	23	27	27	25	27	27	29	27	29	31	28	32	32	35	23
(36)	21	25	17	24	31	23	22	24	23	17	19	25	22	22	22	25	20
(37)	30	30	25	29	25	29	32	34	25	18	23	27	26	20	26	20	24
38	29	28	23	31	27	28	30	37	31	30	32	35	37	37	36	38	34
39	29	24	25	30	25	29	30	31	34	32	33	37	34	37	38	39	31
(40)	27	29	20	28	22	27	25	25	21	23	23	30	24	26	26	27	42
41	29	29	26	28	18	27	27	30	29	31	29	31	36	34	32	36	29
(42)	30	32	25	30	28	31	28	34	32	30	27	20	28	28	25	24	28
(43)	32	25	35	30	30	31	32	30	21	24	28	26	29	21	28	27	11
44	29	26	30	23	24	27	27	32	29	32	35	36	37	35	40	38	27
45	31	23	35	28	31	30	32	33	32	35	35	32	34	35	39	37	34
46	24	29	36	30	29	30	28	34	27	29	32	27	33	29	33	32	19
(47)	27	14	28	24	25	28	25	26	30	25	29	29	28	25	29	23	22
(48)	31	24	33	31	31	34	32	35	28	30	28	25	27	25	29	20	19
49	28	25	33	27	29	30	30	31	32	32	34	32	34	34	39	35	14
(50)	28	18	32	24	28	27	31	26	17	18	21	24	27	13	26	24	11

( ) = Animal not pregnant

APPENDIX 7 (continued)

Individual Food Consumption Data (g)

Group 3, Intermediate dose: 500 mg 610 P.kg^{-1}.day

Animal Number	Day of Gestation																
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
51	30	28	34	19	36	32	29	37	34	35	34	35	38	40	39	41	36
52	27	28	26	18	29	24	29	32	35	36	32	36	38	36	38	41	34
53	32	31	34	17	31	29	30	37	38	33	35	39	40	37	39	44	38
(54)	24	25	28	19	24	21	25	27	25	22	24	25	27	21	28	28	29
55	23	24	28	10	26	24	23	28	31	29	17	30	31	28	33	31	31
56	26	26	27	12	29	24	26	29	29	30	28	32	32	30	37	36	37
57	28	26	24	19	33	27	27	26	36	31	29	34	34	32	34	38	32
58	23	26	28	19	26	24	25	27	30	31	25	33	34	35	37	37	30
59	24	24	22	27	24	28	26	31	28	26	27	23	21	26	21	31	22
60	25	26	22	25	20	25	25	27	28	24	28	33	29	33	34	37	28
61	29	31	24	31	27	28	33	42	36	32	32	39	37	37	42	36	32
62	27	24	18	30	23	29	25	29	29	27	30	29	31	30	33	32	25
63	27	29	20	31	23	27	25	28	28	28	27	31	31	31	31	38	23
64	30	24	28	36	33	37	36	42	32	35	34	38	40	39	41	33	32
(65)	29	28	25	30	23	26	26	33	22	18	23	27	25	21	24	29	23
66	30	32	27	33	28	31	31	32	36	34	32	39	41	37	37	43	32
67	34	23	20	34	35	32	34	34	35	34	33	37	42	36	42	32	30
68	21	25	37	28	34	34	35	35	34	35	35	37	34	40	29	33	18
69	23	21	36	28	30	29	36	32	31	35	34	37	36	37	33	32	23
70	28	21	31	27	31	30	31	32	33	31	36	34	33	37	34	34	30
71	35	23	33	30	33	32	37	33	34	35	37	34	36	38	42	32	34
72	26	20	29	21	24	25	25	26	24	28	26	27	26	28	31	29	15
73	27	21	31	24	30	29	34	32	33	32	37	32	34	39	39	32	24
74	28	24	36	23	28	33	32	33	35	42	37	41	40	42	45	35	31
75	30	27	35	30	33	33	35	38	33	38	38	36	34	38	46	36	26

( ) = Animal not pregnant

APPENDIX 7 (continued)

Individual Food Consumption Data (g)

Group 4, High dose: 1000 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Day of Gestation																
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
(76)	24	24	25	11	28	26	27	29	23	17	19	23	24	16	25	28	24
77	30	26	29	20	28	23	23	27	32	31	28	32	33	34	34	37	33
78	27	27	33	15	32	30	33	33	37	38	33	38	44	41	40	50	35
79	30	28	34	22	35	32	31	35	43	34	31	35	39	40	37	41	30
80	28	32	25	24	33	32	36	36	39	40	40	41	41	42	41	43	39
81	28	24	27	17	29	27	29	30	37	33	31	36	34	38	32	40	35
82	25	25	26	18	30	20	30	27	30	27	25	32	28	31	34	32	28
(83)	25	30	29	18	28	26	25	22	24	26	23	25	19	27	26	27	19
84	29	20	26	32	31	33	33	37	36	37	37	38	39	36	42	35	35
85	28	30	24	28	28	33	31	34	34	33	33	32	34	34	38	21	34
86	25	28	25	27	27	29	27	29	33	30	31	32	34	28	35	40	28
87	32	33	27	33	31	34	32	38	37	36	38	37	39	39	44	38	33
88	29	28	22	28	26	26	31	36	33	36	36	37	35	37	41	32	32
(89)	38	19	27	32	31	40	32	34	29	32	32	31	30	24	29	35	30
90	27	33	28	31	29	30	32	38	41	36	39	41	42	40	44	45	32
91	26	27	24	31	28	30	31	33	35	33	33	37	35	35	39	36	28
92	27	26	22	31	23	29	30	33	31	33	31	33	37	31	39	40	33
93	29	21	34	24	28	30	33	33	37	34	37	35	33	33	44	34	19
(94)	27	20	31	23	28	23	32	29	25	22	31	30	28	22	28	28	6
95	29	25	33	30	32	28	34	36	30	33	36	36	35	34	33	31	22
(96)	27	20	28	21	27	25	28	27	28	21	24	27	29	25	26	20	21
97	28	26	33	26	29	29	34	35	34	35	34	35	36	40	41	35	28
(98)	25	19	29	22	27	26	29	26	23	25	28	24	25	24	27	23	15
99	29	25	35	29	27	28	33	27	29	30	36	35	33	29	36	34	32
100	26	22	36	30	32	36	35	35	37	39	39	41	39	44	42	36	24

( ) = Animal not pregnant

APPENDIX 8

610 P
Developmental Toxicity Study in Rats
Individual Pregnancy Data

Group 1, Control: 0 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Corpora Lutea Graviditatis	Total Implant Sites	Early Deaths	Late Deaths	Foetal Deaths	Live Implants	Uterus Weight (g)	Mean Foetal Weight (g) ± SD
1	13	12	0	0	0	12	71	3.59 ± 0.20
2	15	14	6	0	0	8	58	4.41 ± 0.25
3	15	15	1	0	0	14	91	4.23 ± 0.23
4	15	14	1	0	0	13	84	4.26 ± 0.30
5	8	6	2	0	0	4	26	3.54 ± 0.78
6	16	16	0	0	0	16	96	3.79 ± 0.25
7	16	13	0	0	0	13	77	4.05 ± 0.20
8	14	14	0	0	0	14	88	3.89 ± 0.19
9	14	13	2	0	0	11	77	4.59 ± 0.25
10	14	13	0	0	0	13	84	4.08 ± 0.22
11	14	14	1	0	0	13	86	4.51 ± 0.23
12	14	13	0	0	0	13	77	3.79 ± 0.28
13	12	12	2	0	0	10	65	4.08 ± 0.49
14	16	13	0	0	1	12	77	3.76 ± 0.20
15	14	14	0	0	0	14	89	4.01 ± 0.34
16	12	12	0	0	0	12	74	4.01 ± 0.29
17	15	15	0	0	0	15	93	4.28 ± 0.28
18	16	16	0	0	0	16	97	3.86 ± 0.15
19	17	12	2	0	0	10	65	3.94 ± 0.23
20	16	15	0	0	0	15	89	3.89 ± 0.22
21	14	13	0	0	0	13	74	3.75 ± 0.35
22	13	11	0	0	0	11	NR	4.21 ± 0.35
23	12	9	0	0	0	9	63	4.21 ± 0.39
24	16	16	1	0	0	15	101	4.02 ± 0.21
25	14	12	0	1	0	11	74	4.27 ± 0.25

NR = Not recorded
SD = Standard deviation

APPENDIX 8 (continued)

Individual Pregnancy Data

Group 2, Low dose: 100 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Corpora Lutea Graviditatis	Total Implant Sites	Early Deaths	Late Deaths	Foetal Deaths	Live Implants	Uterus Weight (g)	Mean Foetal Weight (g) ± SD
26	14	12	0	0	0	12	81	4.21 ± 0.29
27	15	14	0	0	0	14	90	4.02 ± 0.30
28	14	14	0	0	0	14	91	4.10 ± 0.24
29	15	14	1	0	0	13	86	4.17 ± 0.24
30	13	13	0	0	0	13	88	4.27 ± 0.26
31	17	16	2	0	0	14	90	4.25 ± 0.23
32	16	14	0	0	0	14	87	4.09 ± 0.20
33	a	14	2	0	0	12	NR	4.08 ± 0.13
34	13	13	1	0	0	12	81	4.38 ± 0.36
35	14	13	0	0	0	13	80	3.93 ± 0.22
(36)	0	0	-	-	-	-	-	-
(37)	0	0	-	-	-	-	-	-
38	14	14	0	1	0	13	79	3.82 ± 0.21
39	16	14	1	0	0	13	86	4.22 ± 0.21
(40)	0	0	-	-	-	-	-	-
41	15	15	2	0	0	13	81	4.25 ± 0.21
(42)	0	0	-	-	-	-	-	-
(43)	0	0	-	-	-	-	-	-
44	16	16	1	0	0	15	89	3.85 ± 0.21
45	13	13	1	0	0	12	79	4.07 ± 0.15
46	12	8	1	0	0	7	49	4.35 ± 0.15
(47)	0	0	-	-	-	-	-	-
(48)	0	0	-	-	-	-	-	-
49	15	15	0	1	0	14	85	3.71 ± 0.18
(50)	0	0	-	-	-	-	-	-

( ) = Animal not pregnant
a = Only 13 counted
NR = Not recorded
SD = Standard deviation

APPENDIX 8 (continued)

Individual Pregnancy Data

Group 3, Intermediate dose: 500 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Corpora Lutea Graviditatis	Total Implant Sites	Early Deaths	Late Deaths	Foetal Deaths	Live Implants	Uterus Weight (g)	Mean Foetal Weight (g) ± SD
51	16	16	0	0	0	16	93	3.75 ± 0.24
52	11	10	0	0	0	10	68	4.11 ± 0.22
53	14	14	2	0	0	12	90	4.75 ± 0.20
(54)	0	0	-	-	-	-	-	-
55	11	11	0	0	0	11	73	3.89 ± 0.30
56	16	6	0	0	0	6	43	4.41 ± 0.29
57	17	15	3	1	0	11	63	3.80 ± 0.29
58	16	16	0	0	0	16	104	4.01 ± 0.26
59	3	1	0	0	0	1	7	2.93
60	11	11	1	0	0	10	67	4.15 ± 0.51
61	17	14	2	0	0	12	81	4.33 ± 0.16
62	13	12	0	0	0	12	80	4.31 ± 0.28
63	12	12	0	0	0	12	82	4.33 ± 0.24
64	15	15	0	0	0	15	97	4.30 ± 0.25
(65)	0	0	-	-	-	-	-	-
66	14	14	0	0	0	14	96	4.32 ± 0.39
67	16	15	1	0	0	14	93	4.29 ± 0.26
68	14	14	1	0	0	13	85	4.20 ± 0.24
69	15	15	1	0	0	14	94	4.04 ± 0.26
70	10	8	1	0	0	7	50	4.30 ± 0.26
71	14	13	0	0	0	13	90	4.29 ± 0.28
72	12	12	0	0	0	12	74	3.77 ± 0.12
73	13	13	1	0	0	12	80	4.21 ± 0.32
74	15	13	1	0	0	12	76	3.62 ± 0.27
75	14	14	1	1	0	12	79	4.00 ± 0.20

( ) = Animal not pregnant
SD = Standard deviation

APPENDIX 8 (continued)

Individual Pregnancy Data

Group 4, High dose: 1000 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Corpora Lutea Graviditatis	Total Implant Sites	Early Deaths	Late Deaths	Foetal Deaths	Live Implants	Uterus Weight (g)	Mean Foetal Weight (g) ± SD
(76)	0	0	-	-	-	-	-	-
77	13	13	0	0	0	13	87	4.49 ± 0.24
78	15	14	1	0	0	13	80	3.72 ± 0.23
79	17	15	0	0	0	15	96	4.21 ± 0.28
80	11	11	0	0	0	11	72	4.05 ± 0.24
81	14	13	2	0	0	11	74	3.83 ± 0.32
82	16	15	0	0	0	15	92	3.95 ± 0.17
(83)	0	0	-	-	-	-	-	-
84	11	11	0	1	0	10	68	4.16 ± 0.22
85	17	14	0	0	0	14	86	3.86 ± 0.23
86	16	14	0	0	0	14	83	3.67 ± 0.13
87	12	12	2	0	0	10	61	3.69 ± 0.23
88	11	11	4	0	0	7	56	4.69 ± 0.26
(89)	0	0	-	-	-	-	-	-
90	14	13	0	0	0	13	96	4.41 ± 0.19
91	13	13	3	1	0	9	65	4.58 ± 0.19
92	13	13	0	0	0	13	76	3.70 ± 0.26
93	12	12	0	0	0	12	83	4.31 ± 0.37
(94)	0	0	-	-	-	-	-	-
95	14	11	1	1	0	9	70	3.51 ± 0.33
(96)	0	0	-	-	-	-	-	-
97	13	12	0	0	0	12	81	4.06 ± 0.22
(98)	0	0	-	-	-	-	-	-
99	13	13	0	0	0	13	82	3.76 ± 0.23
100	13	13	0	0	0	13	83	4.16 ± 0.29

( ) = Animal not pregnant
SD = Standard deviation

APPENDIX 9

610 P

Developmental ~~Toxicity~~ Study in Rats

Individual Incidence of Foetal Abnormalities and Variants

Notes:

Only those foetuses/litters with abnormalities/variants are listed. All other foetuses/litters examined in the study had no abnormalities detected.

Major, deleterious (or potentially deleterious) abnormalities appear in capital letters.

A dash (-) in the 'skeletal' and 'ribs' column indicates that the foetus was preserved in Bouin's fluid and was not examined skeletally.

Foetuses with supernumerary rib(s) are categorised according to the length of the longest supernumerary rib.

Abbreviations used:

NAD = No abnormality detected

a = 13th reduced rib

b = 13 complete ribs

c = 14th vestigial supernumerary rib(s)

APPENDIX 9 (continued)

Individual Incidence of Foetal Abnormalities and Variants

Group 1, Control: 0 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Foetus Number /Sex/ Weight (g)	Abnormality		
		Visceral	Skeletal	Ribs
1	6♂ 4.90	Dilated ureters	-	-
2	7♂ 4.78	Dilated right ureter	-	-
5	2♀ 4.12	Dilated left ureter	-	-
11	2♀ 4.50	Dilated left ureter	-	-
	7♂ 4.35	Abnormal lobation of liver	NAD	b
	10♀ 4.46	Subdural haemorrhage left cerebral hemisphere	-	-
12	7♂ 3.19	Dilated right ureter	-	-
	10♀ 3.46	-	HUNCHED POSTURE WITH DISTORTED CLAVICLES AND RIBCAGE, FLEXURE OF FORELIMBS	b
18	6♀ 3.83	NAD	Sutural bone between left parietal and interparietal	b
19	8♀ 3.84	Hepatic haemorrhage within median liver lobe	-	-
21	4♀ 3.83	Intra-abdominal haemorrhage	-	-
	8♂ 3.96	Haemorrhage on right pinna	-	-
22	1♂ 4.50	Dilated left ureter	-	-
	3♂ 4.40	Increased right renal pelvic cavitation Dilated right ureter	-	-
23	6♂ 4.13	Thin diaphragm with protrusion of median liver lobe	-	-
24	10♂ 4.29	NAD	Misshapen 6th sternebra	b
	11♂ 4.25	Dilated left ureter	-	-
25	4♀ 4.44	Intra-abdominal haemorrhage	-	-

APPENDIX 9 (continued)

Individual Incidence of Foetal Abnormalities and Variants

Group 2, Low dose: 100 mg 610 $P.kg^{-1}.day^{-1}$

Animal Number	Foetus Number /Sex/ Weight (g)	Abnormality		
		Visceral	Skeletal	Ribs
26	12♀ 4.48	NAD	Left cervical rib Minimal distortions of 10th-12th bilateral ribs	c
27	11♀ 3.87	NAD	Sutural bone between left parietal and interparietal	b
31	2♂ 4.54	Dilated left ureter	-	-
	10♂ 4.29	Medial displacement of right testis	-	-
32	8♀ 4.09	Abnormal lobation of liver	NAD	b
33	8♀ 4.00	Hepatic haemorrhage within median liver lobe Intra-abdominal haemorrhage	-	-
	10♀ 4.35	Hepatic haemorrhage within median liver lobe Intra-abdominal haemorrhage	-	-
	12♂ 4.22	Intra-abdominal haemorrhage	-	-
34	2♂ 4.49	NAD	Misshapen 6th sternebra	b
	5♀ 3.59	Small interventricular septal defect	-	-
	6♂ 4.15	Haemorrhagic ring around base of tail	NAD	b
	9♂ 4.21	Testes not fully descended to pelvic position	-	-
35	3♀ 3.80	NAD	Right cervical rib	b
38	1♀ 3.42	Haemorrhage on cranium	-	-
	3♂ 3.90	Haemorrhagic ring in terminal caudal region	NAD	b
39	10♂ 4.42	Hepatic haemorrhage within median liver lobe	-	-
41	2♂ 4.36	Haemorrhage on mandible	-	-
46	6♀ 4.30	NAD	Right cervical rib Sutural bone between left parietal and interparietal	b

APPENDIX 9 (continued)

Individual Incidence of Foetal Abnormalities and Variants

Group 3, Intermediate dose: 500 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Foetus Number /Sex/ Weight (g)	Abnormality		
		Visceral	Skeletal	Ribs
51	2♂ 3.82	Hepatic haemorrhage	-	-
	7♀ 3.39	Haemorrhagic ring in caudal region	NAD	b
	8♂ 3.65	Left testis not fully descended to pelvic position	-	-
52	2♂ 4.20	NAD	DISTORTED 6-11TH RIGHT RIBS Minimally distorted 4th right rib	b
57	4♂ 3.83	Small right eye	-	-
	8♂ 4.23	Hepatic haemorrhage within median liver lobe	-	-
59	1♀ 2.93	ABSENT NASOLABIAL SULCUS; PROTRUDING TONGUE; POSTERIOR CLEFT PALATE; CERVICAL OEDEMA. Haemorrhage in dorsal lumbar region	SHORTENED/BROADENED MUZZLE REGION DOMED CRANIUM IN DORSALLY DISPLACED FRONTAL REGION WITH FLATTENED CRANIAL - CAUDAL ASPECT TO PARIETAL, INTERPARIETAL AND OCCIPITAL REGION; SMALL CRANIAL VAULT DORSAL DISPLACEMENT OF DISTORTED ORBITAL SOCKETS AND ZYGOMATIC ARCHES MISALIGNED/MALROTATED UPPER JAW, LOWER JAW AND (REDUCED) PALATINE BONES MALROTATED HINDLIMBS	b
60	3♂ 3.16	LEFT MICROPTHALMIA	-	-
	8♀ 4.09	NAD	Misshapen 6th sternebra	b
61	4♀ 4.28	Intra-abdominal haemorrhage	-	-
	12♂ 4.47	Haemorrhage on right hindlimb	-	-
62	8♂ 4.33	NAD	Sutural bone between right parietal and Interparietal	c
63	9♀ 3.95	NAD	Bilateral cervical rib	b
	12♂ 4.29	Haemorrhage on left hind foot	-	-

APPENDIX 9 (continued)

Individual Incidence of Foetal Abnormalities and Variants

Group 3, Intermediate dose: 500 mg 610 $P.kg^{-1}.day^{-1}$

Animal Number	Foetus Number /Sex/ Weight (g)	Abnormality		
		Visceral	Skeletal	Ribs
66	1♂ 3.87	Dilated left ureter	-	-
	7♂	Abnormal lobation of liver	-	-
67	6♂ 4.62	Haemorrhage in ventral cervical region	-	-
	12♀ 4.26	Intra-abdominal haemorrhage	-	-
68	5♂ 4.05	Haemorrhage in mandible region	-	-
71	5♂ 4.29	Increased right renal pelvic cavitation	NAD	b
72	2♂ 3.80	Haemorrhage on left hindlimb	NAD	b
75	8♂ 3.91	Subdural haemorrhage right cerebral region	-	-

APPENDIX 9 (continued)

Individual Incidence of Foetal Abnormalities and Variants

Group 4, High dose: 1000 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Foetus Number /Sex/ Weight (g)	Abnormality		
		Visceral	Skeletal	Ribs
78	3♀ 3.83	Hepatic haemorrhage within median liver lobe	-	-
	10♂ 3.55	NAD	Asymmetric pelvic girdle - slight cranial pelvic shift	b
81	8♂ 4.08	Dilated left ureter	-	-
82	13♀ 3.92	Small left thyroid	-	-
	14♀ 4.00	Enlarged left ventricle	NAD	b
85	2♀ 3.82	RETRO-OESPHOGEAL RIGHT SUBCLAVIAN ARTERY	-	-
	6♀ 3.54	INTERVENTRICULAR SEPTAL DEFECTS	-	-
86	14♀ 3.67	NAD	Left cervical rib	c
90	7♂ 4.40	Intra-abdominal haemorrhage	-	-
	8♀ 4.32	NAD	Right cervical rib	b
	10♂ 4.31	NAD	Minimal distortions 7-11th right ribs	b
	11♀ 4.15	Intra-abdominal haemorrhage	-	-
92	4♂ 3.78	NAD	Right cervical rib	c
	5♀ 3.06	Dilated left ureter	-	-
	12♀ 3.54	NAD	Bilateral cervical rib	b
93	2♀ 3.42	Absent innominate artery	-	-
	4♀ 4.22	Protrusion of median liver lobe	-	-
	9♀ 4.25	NAD	Sutural bone between left parietal and interparietal	b

APPENDIX 9 (continued)

Individual Incidence of Foetal Abnormalities and Variants

Group 4, High dose: 1000 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Foetus Number /Sex/ Weight (g)	Abnormality		
		Visceral	Skeletal	Ribs
95	1♂ 3.03	Haemorrhage in nasal region	NAD	b
	69 3.52	Thin diaphragm with protrusion of median liver lobe	-	-
	8♂ 3.47	Left testis not fully descended to pelvic position	-	-
99	5♂ 3.98	DILATED DUCTUS ARTERIOSUS; PULMONARY TRUNK AND ASCENDING AORTA APPEAR TO ARISE FROM RIGHT VENTRICLE; INTERVENTRICULAR SEPTAL DEFECT	-	-
	6♂ 3.46	-	HUNCHED POSTURE WITH DISTORTED CLAVICLES AND RIBCAGE, FLEXURE OF FORELIMBS	c
	109 3.28	Abnormal lobation of liver	HUNCHED POSTURE WITH DISTORTED CLAVICLES AND RIBCAGE, FLEXURE OF FORELIMBS	c

APPENDIX 10

610 P

Developmental Toxicity Study in Rats

Litter Incidences of Number of Ribs

Number of Ribs

a = Reduced 13th rib

b = 13 complete rib(s)

c = 14th vestigial supernumerary rib(s)

Foetuses with supernumerary rib(s) are categorised according to the length of the longest supernumerary rib present

APPENDIX 10 (continued)

Litter Incidences of Number of Ribs

Group 1: 0 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Ribs		
		a	b	c
1	6	0	6	0
2	4	0	4	0
3	7	0	7	0
4	6	0	6	0
5	2	0	2	0
6	8	0	7	1
7	7	0	7	0
8	7	0	7	0
9	6	0	6	0
10	6	0	5	1
11	7	0	6	1
12	6	0	6	0
13	5	0	2	3
14	6	0	6	0
15	7	0	5	2
16	6	0	6	0
17	8	0	7	1
18	8	0	7	1
19	5	0	4	1
20	7	0	6	1
21	7	0	7	0
22	5	0	5	0
23	5	0	5	0
24	7	0	7	0
25	6	0	6	0

Group 2: 100 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Ribs		
		a	b	c
26	6	0	2	4
27	7	0	5	2
28	7	0	7	0
29	7	0	5	2
30	6	0	6	0
31	7	0	6	1
32	7	0	5	2
33	6	0	6	0
34	6	0	5	1
35	7	0	7	0
38	6	0	6	0
39	7	0	7	0
41	7	0	7	0
44	7	0	6	1
45	6	0	6	0
46	3	0	3	0
49	7	0	6	1

APPENDIX 10 (continued)

Litter Incidences of Number of Ribs

Group 3: 500 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Ribs		
		a	b	c
51	8	0	8	0
52	5	0	4	1
53	6	0	5	1
55	6	0	5	1
56	3	0	3	0
57	6	0	6	0
58	8	0	4	4
59	1	0	1	0
60	5	0	5	0
61	6	0	3	3
62	6	0	0	6
63	6	0	2	4
64	7	0	7	0
66	7	0	7	0
67	7	0	1	6
68	6	0	5	1
69	7	0	7	0
70	3	0	1	2
71	7	0	6	1
72	6	0	5	1
73	6	0	4	2
74	6	0	5	1
75	6	0	3	3

Group 4: 1000 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Ribs		
		a	b	c
77	7	1	6	0
78	6	0	6	0
79	8	0	1	7
80	5	0	3	2
81	6	0	3	3
82	7	0	5	2
84	5	0	0	5
85	7	0	2	5
86	7	0	1	6
87	5	0	3	2
88	3	0	1	2
90	6	0	3	3
91	5	0	0	5
92	6	0	3	3
93	6	0	4	2
95	5	0	5	0
97	6	0	6	0
99	7	0	1	6
100	6	0	4	2

APPENDIX 11

610 P

Developmental Toxicity Study in Rats

Litter Incidences of Incomplete Ossification Parameters

Key to Parameter Numbers

Incomplete ossification affecting:

1. ≤3 skull bones
2. ≥4 skull bones
3. Thoracic vertebral centrum(a)
4. 2nd metacarpal(s)/4th metacarpal(s)
5. Pubis(es)
6. Ischium
7. Cervical vertebral arch(es)
8. Lumbar vertebral centra/um
9. Sacral vertebral arch(es)
10. 2nd to 4th metatarsal(s)
11. Unossified 5th metacarpal(s) or 5th metatarsal(s)

APPENDIX 11 (continued)

Litter Incidences of Incomplete Ossification Parameters

Group 1, Control: 0 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Sternebrae Retarded					Parameter number										
		0	1	2	3	>3	1	2	3	4	5	6	7	8	9	10	11
1	6	3	2	1	0	0	1	0	0	0	0	0	0	0	0	0	4
2	4	4	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
3	7	3	4	0	0	0	0	0	0	0	0	0	0	0	0	0	3
4	6	3	2	1	0	0	0	0	0	0	0	0	0	0	0	0	2
5	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
6	8	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	1
7	7	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
8	7	6	0	1	0	0	1	0	0	0	0	0	0	0	0	0	1
9	6	5	1	0	0	0	0	1	0	0	0	0	0	0	3	0	1
10	6	6	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1
11	7	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	6	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	5	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	1
14	6	1	2	3	0	0	0	0	0	0	0	0	0	0	0	0	2
15	7	2	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	6	5	0	0	1	0	0	0	1	0	0	0	0	0	1	0	2
17	8	6	2	0	0	0	1	0	0	0	0	0	0	0	1	0	2
18	8	6	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0
19	5	3	1	1	0	0	2	0	1	0	0	0	0	0	2	0	2
20	7	3	2	2	0	0	3	0	0	0	0	0	0	0	0	0	0
21	7	3	0	4	0	0	4	1	2	1	1	1	0	0	2	0	5
22	5	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
23	5	0	2	3	0	0	1	0	0	0	0	0	0	0	1	0	0
24	7	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	6	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

APPENDIX 11 (continued)

Litter Incidences of Incomplete Ossification Parameters

Group 2, Low dose: 100 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Sternebrae Retarded					Parameter number										
		0	1	2	3	>3	1	2	3	4	5	6	7	8	9	10	11
26	6	6	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
27	7	7	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
28	7	3	3	1	0	0	0	0	0	0	0	0	0	0	0	0	1
29	7	7	0	0	0	0	1	0	1	0	0	0	0	0	0	0	2
30	6	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
31	7	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
32	7	2	3	2	0	0	0	0	0	0	0	0	0	0	0	0	1
33	6	1	5	0	0	0	0	0	3	0	1	0	0	0	1	0	6
34	6	4	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0
35	7	4	1	2	0	0	0	0	0	0	0	0	0	0	0	0	1
38	6	0	5	1	0	0	0	0	0	0	0	0	0	0	0	0	3
39	7	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	7	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	7	2	3	2	0	0	1	1	1	0	0	0	0	0	0	0	2
45	6	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
46	3	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	7	3	4	0	0	0	3	0	1	0	0	0	0	0	3	0	6

APPENDIX 11 (continued)

Litter Incidences of Incomplete Ossification Parameters

Group 3, Intermediate dose: 500 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Sternebrae Retarded					Parameter number										
		0	1	2	3	>3	1	2	3	4	5	6	7	8	9	10	11
51	8	0	3	5	0	0	0	0	0	0	0	0	0	0	0	0	1
52	5	5	0	0	0	0	2	1	0	0	0	0	0	0	2	0	0
53	6	6	0	0	0	0	2	0	2	0	0	0	0	0	0	0	0
55	6	6	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
56	3[a]	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
57	6	0	3	3	0	0	0	0	0	0	0	0	0	0	0	0	3
58	8	3	5	0	0	0	1	1	0	0	0	0	0	0	0	0	0
59	1	0	0	1	0	0	0	1	0	0	0	0	1	0	0	1	1
60	5	4	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
61	6	0	5	1	0	0	0	0	0	0	0	0	0	0	0	0	1
62	6	6	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
63	6	5	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
64	7	4	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0
66	7	5	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
67	7	0	7	0	0	0	5	0	0	0	0	0	0	0	0	0	3
68	6	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
69	7	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70	3	2	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
71	7	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
72	6	1	5	0	0	0	2	0	0	0	0	0	0	0	0	0	0
73	6	3	1	2	0	0	0	0	1	0	0	0	0	0	0	0	2
74	6	1	0	4	0	1	2	1	0	0	0	0	0	0	1	0	6
75	6	2	3	1	0	0	1	0	0	0	0	0	0	0	0	0	0

a = One foetus with damaged sternum - unable to examine

APPENDIX 11 (continued)

Litter Incidences of Incomplete Ossification Parameters

Group 4, High dose: 1000 mg 610 P.kg^{-1}.day^{-1}

Animal Number	Number of Foetuses Examined	Number of Sternebrae Retarded					Parameter number										
		0	1	2	3	>3	1	2	3	4	5	6	7	8	9	10	11
77	7	4	2	1	0	0	0	0	2	0	0	0	0	0	0	0	0
78	6	0	4	2	0	0	0	0	0	0	0	0	0	0	0	0	3
79	8	2	5	1	0	0	3	0	0	0	0	0	0	0	0	0	1
80	5	3	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0
81	6	2	3	1	0	0	2	0	0	0	0	0	0	0	0	0	5
82	7	2	3	2	0	0	0	0	0	0	0	0	0	0	0	0	1
84	5	1	4	0	0	0	1	1	0	0	0	0	0	0	0	0	1
85	7	1	4	2	0	0	0	0	0	0	0	0	0	0	0	0	1
86	7	0	2	5	0	0	0	0	0	0	0	0	0	0	0	0	2
87	5	1	4	0	0	0	1	0	0	0	0	0	0	0	0	0	1
88	3[a]	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
90	6	2	4	0	0	0	1	0	1	0	0	0	0	0	0	0	0
91	5	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	1
92	6	0	6	0	0	0	2	0	0	0	0	0	0	0	1	0	2
93	6	4	2	0	0	0	2	0	0	0	0	0	0	0	0	0	2
95	5	0	1	2	0	2	0	0	1	0	0	0	0	1	0	0	4
97	6	3	2	1	0	0	2	0	0	0	0	0	0	0	0	0	1
99	7	1	1	1	2	2	3	3	0	1	1	1	0	0	1	0	7
100	6	4	0	2	0	0	2	0	0	0	0	0	0	0	0	0	0

a = One foetus with damaged sternum - unable to examine

Triage of 8(e) Submissions

Date sent to triage: 10/25/96 (NON-CAP) CAP

Submission number: 13680 A TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Gordon Cash (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 -HERD (1 copy each)

STOX CTOX EPI (RTOX) GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.):_____

Notes:

☒ This is the **original** 8(e) submission; refile after triage evaluation.

☐ This **original** submission has been **split**; rejoin after triage evaluation.

☐ Other:

Photocopies Needed for Triage Evaluation				
entire document:	**0**	**1**	**2**	**3**
front section and CECATS:	**0**	**1**	**2**	**3**

Initials:_____ **Date:**_____

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ-0796-13680 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: CONDEA VISTA

Company

SUB. DATE: 06/25/96 OTS DATE: 07/01/96 CSRAD DATE: 08/20/96

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME: CAS#

1,2-Benzenedicarboxylic acid, DT-C6-10-Alkyl Esters 68515-51-5
WITAMOL 110/LINPLAST 610P "
VISTA 610P Plasticizer "

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	(0243)	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
(0207)	REPRO/TERATO (ANIMAL)	(1) 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQEST DELAY	01 02 04	(0248)	PROD/USE/PROC	01 02 04
0209	NEURO (ANIMAL)	01 02 04	(0224)	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0299	OTHER	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
0212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
0213	SUB ACUTE TOX (ANIMAL)	01 02 04	0228	ALLERG (ANIMAL)	01 02 04			
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
0215	CHRONIC TOX (ANIMAL)	01 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	RAT	LOW	~~developmental~~	
CAS SR	NO	NO (CONTINUE)		MED	Plasticizer	
	DK TO ADMIN	REFER		HIGH		

COMMENTS